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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,638	02/08/2002	Tim Wilhelm Nattkemper	HSS-021XX	5891

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EXAMINER	
LAVIN, CHRISTOPHER L	
ART UNIT	**PAPER NUMBER**
2621	

DATE MAILED: 10/18/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,638	NATTKEMPER ET AL.	
	Examiner	Art Unit	
	Christopher L. Lavin	2621	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment

This action is in response to the amendment received on 08/05/05.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 1 – 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In steps d and e, the applicant claims feature combinations. This is not disclosed in the specification. In page 8 of the specification the applicant claims that a PCA transform is performed which results in determining characteristics features. However there is nothing that mentions or describes combining these features. As the feature combinations are part of OR statements the examiner does not need to address them in the rejection shown below.

Step d recites "to a classification value between 0 and 1". However the specification, page 9 first full paragraph, discloses that the feature sets are set to either 1 or 0 no values are set that are between these two numbers. The uncertainties in this claim rises to the level of a 35 U.S.C. 112 rejection because of the inconsistency between the claimed subject matter and the specification (See MPEP 2173.03). For the purpose of this action the examiner will assume the specification is correct.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 1 – 3, 6 – 12, and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luck (5,257,182) in view of Watanabe (5,522,015).

7. In regards to claim 1 Luck discloses a method for analyzing microscope images comprising of the following steps:

a) Taking at least two microscope images of a sample including a plurality of biological objects (col. 4, lines 13 – 19);

b) Selecting a first microscope image and marking the positions (s) of mass gravity centers, i.e., centroids, of a number n of the individual objects discernible in the first microscope image, in which step each marked object is assigned a defined first image excerpt which completely surrounds the marked object, and each first image excerpt including a marked object, and each first image excerpt including a marked object is assigned the value 1, with the number n of such marked first image excerpts constituting a positive training set (col. 7, lines 46 – 53; col. 13, lines 17 – 23: Two training sets are disclosed, malignant and benign with a 0.9 and 0.1. Luck does not disclose using 1 and 0 for training a neural network. This will be shown to be well known in the art through Watanabe below. A complete training set consists of a positive (1) and a negative (0) training set; col. 13, lines 40 – 48: the training set is based on "precisely the same type of net images" as were obtained for classification.);

c) Selecting and marking a number m of second image excerpts each spaced a predetermined minimum distance from said first image excerpts, with a second image excerpt corresponding in size and shape to said first image excerpt, in which step each second image excerpt is assigned the value 0, with the number m of such marked second image excerpts constituting a negative training set (col. 7, lines 46 – 53; col. 13, lines 17 – 23; col. 8, lines 49 – 62; col. 13, lines 40 – 48: Two training sets are

disclosed, malignant and benign with a 0.9 and 0.1. The training excerpts are chosen in exactly the same manner as the excerpts to be analyzed. Luck discloses that the image is processed to remove all objects larger than the objects of interest. So cell clumps will be removed; thus the only thing that will remain in the image after the processing is individual cells. Therefore cells that are touching would not remain. So only separate cells (at least 1 pixel of separation) will remain in the image, and therefore a minimum predetermined distance (1 pixel) is maintained between the first image excerpts and the second image excerpts.);

d) Determining characteristic features and/or feature combinations of the positive and negative training sets and assigning said characteristic features and/or feature combinations to a classification value between 0 and 1, said classification value representing the degree of probability of the presence of a marked object, and the determined features and/or feature combinations are stored (col. 13, lines 57 – 64: The neural network will analyze characteristic features such as shape, size, and gray scale, which are features, and not the actual image itself.);

e) Determine classification values of all image points of the second and each further microscope image by comparing the image data of the second and each further microscope image with the features and/or feature combinations determined in procedural step d), in which step, for each image point of the second and each further microscope image, the classification value for an image excerpt surrounding the image point is determined and the size and shape of this image excerpt corresponds to the size and shape of the first or second image excerpt (col. 13, lines 17 – 23);

Luck (as modified by Watkin) does not disclose using 1 and 0 for training a neural network. However, Watanabe (col. 5, lines 59 – 61) discloses using 1 and 0 to train a neural network. Luck discloses a method capable of classifying biological specimens on a microscope slide, however Luck has not specifically claim a threshold. However, Watanabe (col. 25, lines 42 – 44) discloses using a threshold of 0.5 to separate neural network outputs into two possibilities.

Therefore it would have been obvious to one having ordinary skill in the art at the time of the invention to use 0 and 1 to train a neural network as taught by Watanabe instead of 0.1 and 0.9 as taught by Luck (as modified by Watkin). As the intent is to separate two types allowing more separation between the types will allow for better thresholding. Also to use thresholding for classification of neural network outputs (as disclosed by Watanabe) in the method disclosed by Luck (as modified by Watkin) allows for separation of the data into two subsets, as Luck's method is designed to classify a cell as either malignant or benign thresholding will quickly and easily separate outputs for easy analysis.

8. With regards to claim 2, the method as claimed in claim 1 wherein the sample is a tissue sample and the biological object is a cell (Luck, col. 8, lines 33 – 35).

9. With regards to claim 3, the method as claimed in claim 1 wherein the biological objects to be determined are marked with one or plural chemical markers before the microscope images are taken (Luck, col. 8, lines 33 – 35).

10. With regards to claim 6, the method as claimed in claim 1 wherein the microscope images are taken by a CCD camera and then digitized (Luck, col. 7, lines 11 – 13).

11. With regards to claim 7, the method as claimed in claim 1 wherein the number n of the individual biological objects marked in procedural step b) is larger than or equal to 50 (Luck, col. 13, lines 17 –19: As "several hundred or thousands" of cells are used to create a training set inherently at least 50 of these biological objects would represent the positive (malignant) case.).

12. With regards to claim 8, the method as claimed in claim 1 wherein the first image excerpt is of square shape, with the size and/or side length of the first image excerpt corresponding at least to the maximum diameter of the biological objects in the first microscope image (Luck, col. 7, lines 49 – 59).

13. With regards to claim 9, the method as claimed in claim 1 wherein the number n of second image excerpts is larger than or equal to 50, with the second image excerpts being defined automatically, keeping to the minimum distance from the respective first image excerpts (Luck, col. 13, lines 17 – 19: As "several hundred or thousands" of cells are used to create a training set inherently at least 50 of these biological objects would represent the negative (begin) case; Watkin, third paragraph on page 529).

14. With regards to claim 10, the method as claimed in claim 1 wherein classification values of all image points of the second and each further microscope image are automatically determined according to procedural step e) by scanning the image surface of the second and each further microscope image (Luck, col. 14, lines 3 – 7).

15. With regard to claim 11, the method as claimed in claim 1 wherein the threshold value of the classification value representing the presence of a biological object is at least 0.5 (Watanabe, Col. 25, lines 42 – 44).

16. With regards to claim 12, the method as claimed in claim 1 wherein the object positions determined by procedural steps a) to f) are compared in the total number of microscope images so as to obtain a spatial location and distribution of the individual objects in the sample (Luck, col. 14, lines 30 – 35).

17. With regards to claim 14, the method as claimed in claim 2 wherein the biological objects to be determined are marked with one or plural chemical markers before the microscope images are taken (Luck, col. 8, lines 33 – 35).

18. Claims 4, 5, 13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Luck (as modified by Watanabe) as applied to claim 3 above, and further in view of Hemstreet (5,733,721).

Luck discloses a method for analyzing a microscope slide containing biological cells (col. 5, lines 16 – 21). Luck however does not teach how to prepare that slide or that fluorochrome should be used to mark the slide.

Hemstreet teaches that slides should be rinsed (col. 28, lines 27 – 32) before staining. Hemstreet then teaches that to create fluorescent images requires staining the slide with a fluorchrome (col. 7, line 64 – col. 8, line 6). Hemstreet then analyzes the fluorescent images with a neural network (col. 7, lines 47 – 51).

Luke (as modified by Watanabe) and Hemstreet are combinable because they are from the same field of endeavor, i.e., using neural networks to classify biological

cells. It would have been obvious to one having ordinary skill in the art at the time of the invention to prepare and stain the microscope slide (as taught by Hemstreet) before analyzing the microscope slide (as taught by Luke). A slide needs to be prepared in advance of use if the results are to be trusted. By staining the slide the method disclosed by Luke will have an easier time of identifying cells of interest.

19. With regards to claim 4, the method as claimed in claim 3 wherein the objects to be determined are marked with one or plural chemical markers before the microscope images are taken, with a bleaching or rinsing procedure being performed between the taking of the individual microscope images (Hemstreet, col. 28, lines 27 – 32).

20. With regards to claim 5, the method as claimed in claims 3 wherein said chemical markers are fluorochrome markers and the microscope images are fluorescence images (Hemstreet, col. 7, line 64 – col. 8, line 6).

21. With regards to claim 13, use of a method as claimed in claim 1 for the automatic cell classification of fluorescent cells (Luck, col. 3, lines 38 – 39; Hemstreet, col. 7, line 64 – col. 8, line 6).

22. With regards to claim 15, the method as claimed in claim 4 wherein said chemical markers are fluorochrome markers and the microscope images are fluorescence images (Hemstreet, col. 7, line 64 – col. 8, line 6).

Response to Arguments

23. Applicant's arguments, see page 9, line 13 – page 10, line 15, filed 09/22/05, with respect to the rejection(s) of claim(s) 1-15 under 103 have been fully considered and

are persuasive. Therefore, the rejection has been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Luck and Watanabe.

In particular the applicant is correct the examiner incorrectly applied Watkin to the reference. In fact upon further consideration the examiner has discovered that Luck already disclosed the material Watkin was used to teach. The examiner apologizes for the mistake.

24. The applicant argues that, "Luck discloses classifying cells based on their morphology and not by recognition of their position(s)".

The examiner has carefully read and reread the specification and cannot find any support for this assertion. The specification teaches that a PCA transform is performed and the resulting 6 dimensional object is used in the neural network. This has nothing to do with position, but in fact is based on morphological features.

25. The applicant states that, "previously performed training, which is not described".

Luck does indeed disclose how the training works. As shown above Luck states that the training images are prepared exactly as the images that are analyzed. Luck also discloses that a neural network is used. How a neural network is trained is well known in the art.

26. The applicant argues that there is not relationship between the training in Luck and the use of the training on the second and subsequent images.

First the claim does not require only a single image for training. Luck as pointed out has a training set of at least several hundred. Luck does not state if this is from a single image or multiple images, regardless though this does not matter as Luck uses

the same approaches to obtain the training images as the images to be analyzed. Clearly more then one training image excerpt from each slide must be obtained for practical purposes.

Second, Luck clearly states that the training set is then used to identify the analyzed excerpts. Therefore there is a relationship between training and classifying.

Finally, all objects are identified either as normal abnormal or not a cell by the end of the classification process.

27. The applicant points out that the examiner does not mention step f in his rejection.

However step f was not mentioned because a 103 was needed to deal with the subject matter of step f. That said Luck clearly identifies the positions of the biological objects as the cells are identified and the positions of those cells are known. The concept of a threshold is well known in neural networks as shown by Wantanabe.

28. The applicant finally argues that Wantanabe does not teach the concepts the examiner claims it teaches.

It is the examiner's belief that much of the confusion with this case is the applicant's belief that the claimed invention has two training sets. In neural networks a training sets consists of examples of yes (1) and no (0) cases. Thus the "positive training set", claimed by the applicant, is only half of a full training set. Luck discloses a complete training set. In fact the examiner would like to point the applicant to the applicant's own specification page 9, lines 5 – 8 where the applicant also claims one variable, y, which can have two different values (1 or 0).

If the applicant truly had two training sets there would be two complete training sets. For example, the "positive training set" would have examples of yes and no cases and not simply yes cases. The same is true for the "negative training set". And then only one of these training sets would be used to analyze an image. For example, the applicant might have created a training set used for a particular type of marker and a second training set for another type of marker. Then when the slide to be analyzed is treated with the first marker the first training set would be used. This is not what the applicant is claiming.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher L. Lavin whose telephone number is 571-272-7392. The examiner can normally be reached on M - F (8:30 - 5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mancuso Joseph can be reached on (571) 272-7695. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Christopher Lavin

BRIAN WERNER
PRIMARY EXAMINER